IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Daniel Kahne, et al.

Application No.: 10/631,883 **Group Art Unit:** 1639

Filing Date: July 31, 2003 **Examiner:** Jeffrey S. Lundgren

For: Glycopeptide Antibiotics, Combinatorial Libraries of Glycopeptide Antibiotics, and Methods for Producing Same

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

DECLARATION OF DANIEL KAHNE, Ph.D.

I, Daniel Kahne, hereby declare that:

1) I am an inventor of U.S. Patent Application Serial No. 10/631,883, ("the 883 patent application") filed July 31, 2003, and claiming priority to U.S. Application No. 09/353,368, filed July 14, 1999, which claims benefit of Provisional Application Serial No. 60/134,839 filed May 19, 1999, and benefit of U.S. Patent Application No. 09/115,667, filed July 14, 1998 (converted to Provisional Application No, 60/150,690).

2) I received a Bachelor of Arts degree from Cornel University in 1981. In 1986, I received a Doctor of Philosophy degree in Organic Chemistry from Columbia University. From 1988 to 2004, I worked as a professor at Princeton University, including as an Assistant Professor of Chemistry (1988-1991), Associate Professor of Chemistry (1991-1994), Professor of Chemistry (1994-2000), and an A. Barton Hepburn Professor of Organic Chemistry (2000-2004). Since 2004 I have worked for Harvard University in the Department of Chemistry and Chemical Biology as a Professor of Chemistry and Chemical Biology (Harvard University) and as a Professor of Biological Chemistry and Molecular Pharmacology (Harvard Medical School). A copy of my *Curriculum Vitae* and list of publications is attached as Attachment 1.

3) I understand that the Patent Office has asserted that claims 1, 5-11, 14-23, 26-32, 35-38, and 102-116 contain subject matter that lacks adequate written description and enablement under 35 U.S.C. § 112, first paragraph such that the subject matter of the pending claims was not described in the July, 2003 patent application in such a way as to reasonably convey to those skilled in the art that the inventors had possession of the claimed subject matter.

4) I do not agree with the Patent Office that the subject matter defined by claims 1, 5-11, 14-23, 26-32, 35-38, and 102-116 is not described in the 883 patent application. In particular, I disagree with the Office's assertion that the pending claims lack written description. I understand that the standard by which written description is evaluated is whether the patent specification describes the invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention.

5) The 883 patent application describes a class of novel glycopeptides. The glycopeptides contain a core peptide structure of the formula A_1-A_2-A_3-A_4-A_5-A_6-A_7, in which each dash represents a covalent bond, where each of the groups A_1 to A_7 comprises an _-amino acid residue. Furthermore, the group A_1 is linked to an amino group on the group A_2, each of the groups A_2, A_4 and A_6 contains an aromatic side chain, which aromatic side chains are cross-linked together by two or more covalent bonds, and the group A_7 bears a terminal carboxyl, ester, amide, or N-substituted amide group. This core peptide structure resembles the peptide structure found in naturally occurring vancomycin, but as claimed, the peptide portion is not limited to the peptide structure found in naturally occurring vancomycin.

The glycopeptides of the 883 patent application are further defined such that the group A_4 is linked via a glycosidic bond to a disaccharide. That disaccharide is described as having a glucose residue directly attached to the A_4 residue, and that glucose residue further bears an N-substituted aminohexose residue and at least one substituent of the formula YXR. The substituent is described as being attached to the C-6 position of the glucose. The 883 patent application also describes the composition of the substituents, that is, the group Y is a single bond, O, NR_1 or S; the group X is O, NR_1, S, SO_2, C(O)O, C(O)S, C(S)O, C(S)S, $C(NR_1)O$, $C(O)NR_1$, or halo (in which case Y and R are absent); and R, R_1, R_2, and R_3 are independently hydrogen, alkyl, aryl, aralkyl, alkanoyl, aroyl, aralkanoyl, heterocyclic,

heterocyclic-carbonyl, heterocyclic-alkyl, heterocyclic-alkyl-carbonyl, alkylsulfonyl or arylsulfonyl; and any pharmaceutically acceptable salts thereof; provided that at least one of the substituent of the formula YXR is not hydroxyl; X and Y are not both O; X and Y are not S and O, or O and S, respectively; and if two or more of said substituent are present, they can be the same or different.

6) The 883 patent application contains numerous examples that teach how to make the breath of the claimed glycopeptides. For example, examples 18-99 teach how to make a claimed glycopeptide where the peptide portion is aglycon of vancomycin and the substituent attached to the C-6 position of the glucose is a XYR group. Over 40 different XYR groups are described throughout these examples. These numerous examples are summarized in three tables in my application, at pages 131-135. These numerous examples adequately teach one skilled in the art how to make glycopeptide compounds which contain A_4-modified vancomycin attached to the C-6 position of the glucose residue having at least one substituent of the formula XYR. These examples further describe how to make the full scope of the claimed invention.

7) Read as a whole, the 883 patent application describes my invention with sufficient detail so as to put the public to which it is directed in possession of my invention.

8) I also disagree with the Office's assertion that the pending claims lack enablement. I understand that a disclosure is sufficiently enabled if a person of ordinary skill in the art, having the disclosure before them, would be able to make and use the invention without undue experimentation.

9) As described above, the 883 patent application contains numerous examples that teach how to make the breath of the claimed glycopeptides. For example, examples 18-99 teach how to make a claimed glycopeptide where the peptide portion is the aglycon of vancomycin and the substituent attached to the C-6 position of the glucose is a XYR group. These numerous examples are summarized in three tables in my application, at pages 131-135.

10) At the time the 883 application was filed, vancomycin was known to be a glycopeptide antibiotic that kills cells by binding to the D-Ala-D-Ala peptide substrate involved in cross-linking the sugar polymers that comprise the bacterial cell wall. The carbohydrate portion of vancomycin was known not to be directly involved in binding to D-Ala-D-Ala. However, it had been shown by scientists at Lilly that N-alkylation of the

terminal vancosamine sugar with a hydrophobic group increases activity against vancomycin resistant strains dramatically. Vancomycin was also known to be a complex molecule with a diverse array of functionality and its sensitivity to acids, bases, and oxidation was documented. Furthermore, it was known to be soluble only in water and other polar solvents, which were not compatible with chemical glycosylation reactions. Despite the importance of this carbohydrate in biological activity, no efforts to replace the vancosamine with a different sugar had been reported before 1998. In fact, as far as I am aware, the chemical glycosylation of vancomycin at any position had never been achieved before this time. In 1998, I and other scientists added to the general knowledge of the vancomycin field when we published a paper (*Reconstruction of Vancomycin by Chemical Glycosylation of the Pseudoaglycon*, J. Am. Chem. Soc., 1998, 120:11014, attached here as Attachment 2) in which we reported a strategy for glycosylating the pseudoaglycon of vancomycin. This chemistry would permit the synthesis of large numbers of vancomycin derivatives in which the terminal carbohydrate moiety is varied.

11) Based on my understanding of the state of the art at the time the 883 application was filed, combined with what is taught by the 883 specification, the application is sufficiently enabled so that a person of ordinary skill in the art, having the disclosure before them, would be able to make and use the full scope of my invention as claimed without undue experimentation.

12) I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under §1001 of Title 18 of the united Stated Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

6/29/06 _____

Date

Daniel Kahne, Ph.D.